

REMARKS

Each rejection raised by the Examiner is addressed separately below. In view of the remarks discussed below, Applicants respectfully request reconsideration of the merits of this patent application.

Status of the Claims

Claims 1 and 4-17 are pending. Claims 2-3 have been cancelled. Claims 18-23 have been withdrawn. No amendments have been made, and no new matter has been added.

Rejections Under 35 U.S.C. § 103

Claims 1 and 4-17 are rejected under 35 U.S.C. 103(a) as being obvious over Abelson et al. (The Journal of Biological Chemistry, 1998, 273:12685-12688) in view of Diener et al. (Molecular Cell, 1998, 1:883-894) and Reyes et al. (Analytical Chemistry, 1987, 166:90-106).

The Examiner alleged that it would have been obvious to one of ordinary skill in the art to use a conserved, common mechanism for recognizing non-tRNA RNA substrates having a BHB motif to cleave a desired target nucleic acid in view of Abelson and Reyes. The Examiner alleges that Abelson teaches that tRNA endonuclease inherently cleaves the BHB structure of a tRNA substrate and that Reyes teaches cleaving an artificially-synthesized, non-tRNA oligonucleotide substrate that contains the BHB motif, each containing the G/A and U/A dinucleotides. The Examiner argues that one of skill would be motivated to do so because Abelson teaches that the BHB-motif structure-based cleavage of a target RNA oligonucleotide substrate is a conserved, absolute biological mechanism of a tRNA splicing endonuclease which can cleave any "universal" substrate containing the BHB motif, and Reyes teaches that tRNA splicing endonuclease-mediated tRNA cleavage was demonstrated to occur in any synthetic oligonucleotide substrate having proper structures that can be recognized by the tRNA splicing endonuclease. Applicants disagree.

A close review of Abelson shows that Abelson actually teaches that "it is likely that what has been conserved since the divergence of the Eukary and the Archaea is the endonuclease active site and the means to array two of them in a precise and conserved spatial orientation." (Abelson, p. 12688, last paragraph). Abelson cites as support for this "the results of Tocchini-Valentini and co-workers" (specifically, Fabbri et al., Science 280 (1998) 284-286, which has

been addressed in previous responses) "where it is demonstrated that both the eukaryal and archaeal endonucleases can accurately cleave a universal substrate containing the BHB motif." (Abelson, p. 12688, last full paragraph). Accordingly, when the Examiner cites Abelson as teaching that the BHB-motif structure-based splicing or cleavage of a target RNA oligonucleotide substrate is a conserved, absolute biological mechanism of a tRNA splicing endonuclease which can cleave the "universal" BHB substrate, she is actually citing Fabbri.

As discussed in previous responses, Applicants acknowledged that Fabbri disclosed that pre-tRNAs (i.e., a tRNA structure having (1) a 5'-terminal phosphate group; (2) an acceptor stem comprising a seven base pair stem made by the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides; (3) a CCA tail at the 3' end; (4) a D loop comprising a four base pair stem ending in a loop; (5) an anticodon loop comprising a five base pair stem whose loop contains the anticodon; and (6) a T loop comprising a five base pair stem) and mini-substrates having whole, cis-formed BHB motif (including a terminal loop) can be cleaved by not only archaeal endonucleases, but also by eukaryal tRNA endonucleases (see FIGS. 1-2 of Fabbri). However, Fabbri does not contemplate or disclose to one of ordinary skill in the art that a trans-formed BHB motif (lacking a terminal loop) could be cleaved by eukaryal tRNA endonucleases (see, e.g., FIGS. 4 and 13 of the application for transformed BHBs). Thus, in contrast to Fabbri, the claimed methods do not require all the structures present in pre-tRNA for cleavage, which allows one to advantageously cleave non-tRNA molecules.

As previously explained, Fabbri is strictly directed toward cleavage of pre-tRNAs and mini-substrates having a whole, cis-formed BHB motif and does not contemplate or disclose trans-formed BHBs. It was neither known, nor predictable, at the time of Fabbri that a trans-formed BHB could result in cleavage of an RNA molecule by eukaryal tRNA endonucleases. In contrast, the claimed methods are directed toward Applicants' surprising finding that such enzymes can recognize and cleave trans-formed structures having only a BHB motif. Applicants submit that neither Fabbri, nor Abelson, teach or suggest Applicants' surprising finding that a trans-formed BHB could result in cleavage of an RNA molecule by eukaryal tRNA endonucleases and that such enzymes can recognize and cleave trans-formed structures having only a BHB motif.

Nothing in Diener or Reyes corrects this deficiency. Diener is directed to determining the solution structure of the BHB motif by NMR. The Examiner cites Diener as showing the

motif-based splicing of a tRNA substrate because Fig. 1 of Diener shows that the 3' cleavage site of the BHB motif in pre-tRNA contains the U/A dinucleotide, wherein the cleavage occurs between the U and the A, and that the 5' cleavage site of the BHB motif in the pre-tRNA contains the G/A dinucleotide, wherein the cleavage occurs between the G and the A. However, like Fabbri and Abelson, Diener does not teach or suggest that a trans-formed BHB motif (lacking a terminal loop) could be cleaved by eukaryl tRNA endonucleases, as recited in the pending claims.

Reyes is cited by the Examiner as teaching a method of synthesizing an artificial RNA oligonucleotide substrate for in vitro splicing by a tRNA splicing endonuclease, where the artificial substrate has a BHB with the G/A and U/A dinucleotides (i.e., one bulge of the BHB has a guanine/adenine dinucleotide and the other bulge of the BHB has either a uracil/adenine dinucleotide or a thymine/adenine dinucleotide.) However, nothing in Reyes teaches that non-tRNA target RNA can be cleaved by eukaryl endonucleases when the BHB is present in this form.

Accordingly, as none of Abelson, Diener or Reyes, either alone or in combination, teach or suggest that non-tRNA target RNA can be cleaved by eukaryl endonucleases when the BHB has the G/A and U/A dinucleotides, this rejection should be withdrawn.

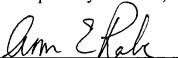
Summary

In view of the above remarks, reconsideration is respectfully requested. A petition for a three-month extension of time accompanies this response so that it will be deemed to have been timely filed. No other extension of time is believed due; however, if any additional extension is due, in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to Deposit Account No. 17-0055. Likewise, no other fee is believed due in connection with this submission. However, if a fee is due, in this or any subsequent response, please charge the fee to Deposit Account No. 17-0055.

Respectfully submitted,

Date: Tuesday, May 12, 2009

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